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Research Article

Protective Effect of *Micromeria congesta* Against LPS-induced Oxidative Stress and Inflammation in Rat Livers

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Abstract

This study aims to investigate the possible effects of *Micromeria congesta* (MC) against inflammation and oxidative damage in the liver caused by Lipopolysaccharide (LPS) used in sepsis modeling. A total of 24 animals, 6 Wistar Albino rats in each group, were used in the study. Animals were assigned to control, LPS, LPS+25 mg/kg MC, LPS+50 mg/kg MC groups. In MC groups plant extract was administered to the animals for 7 days, LPS application was been made on the 7th day and the animals were euthanized 6 hours later. After euthanasia, the liver was examined histopathologically and immunohistochemically. In histopathologic examinations, it was determined that the use of MC at increasing doses against liver toxicity caused by LPS decreased the lesions in the liver. In immunohistochemical examination, it was determined that TNF-α and IL-2 expressions, which are important biomarkers of inflammation, decreased in parallel with the increasing dose compared to the LPS group. In addition, HSP 27 expression, which is a marker of oxidative stress, was also found to decrease with increasing dose of MC extract. It was revealed that MC extract had a protective effect on LPS-induced liver toxicity by reducing inflammation and oxidative stress. More studies are needed for MC to be an alternative in the treatment of sepsis.

Keywords: Inflammation, lipopolysaccharide, liver, *Micromeria congesta*, oxidative stress

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Introduction

Lipopolysaccharide (LPS) is the main component of the cell outer membrane of Gram negative bacteria and is also called endotoxin (Rhee 2014). LPS induces inflammation by stimulating myeloid differentiation protein-2 (MD-2), CD14, toll-like receptor 4 (TLR4) through the LPS binding protein LPB (Mazgaeen and Gurung 2020, Chen et al 2021). LPS also causes oxidative stress by disrupting intracellular redox balance. Oxidative stress and inflammation have mechanisms that induce each other (Al-Dossari et al 2020, Ramos-Tovar and Muriel 2020).

TNF, an important biomarker of inflammation, is a polypeptide pro-inflammatory immune cytokine with important roles in inflammation management, cell differentiation, survival, regulation and apoptosis (Silke and Hartland 2013, Gonzalez Caldito 2023). TNF-α is released by neutrophils, T lymphocytes, fibroblasts and mast cells, smooth muscle cells, basophils, tumor cells, natural killer cells and many other cells in the organism, especially activated macrophages and monocytes (Abdulkhaleq et al 2018, Harvanová et al 2023). Although there are many reasons for the production and release of TNF- α, the main pathologic trigger is lipopolysaccharides (Çayakar 2018, Kara and Ozkanlar 2023). Interleukins are also utilized in the monitoring of inflammation. IL-2 is a proinflammatory cytokine that is transcribed and synthesized by antigen-stimulated T lymphocytes. It stimulates

the proliferation of lymphocytes and macrophages and induces inflammation by activating cytotoxic T cells and natural killer cells (Shaw et al 2018). Heat shock proteins (HSP) are a family of proteins that are present in cells under normal conditions and function as chaperones, but increase in cases of sudden heat, oxidative stress and inflammation (Ikwegbue et al 2017). HSP 27 is a protein in the small heat shock protein class and it is reported that the C-terminal domain has protective activity against oxidative stress and shows anti-apoptotic effect. It has been used as an important oxidative stress biomarker in recent studies (Federico et al 2005, Ghayour-Mobarhan et al 2012).

Micromeria congesta is a plant with antioxidant activity due to its high content of polyphenolic substances (Vladimir-Knežević et al 2011). In addition, volatile fatty acids obtained from this plant extract have anti-inflammatory, anti-microbial, anti-rheumatic and anelgesic properties (Marinković et al 2002, Herken et al 2012). The liver, which has important functions such as the removal of toxic substances in the organism, regulation of metabolism and support of immunity, is highly sensitive to LPS stimulation, and if exposed to it, inflammation is induced and various oxidative products are also released (Zhu et al 2012, Zhou et al 2022).

Natural antioxidants and herbal extracts are known to prevent these pathological processes (Stickel and Schuppan 2007, Amat et al 2010, Hatipoglu et al 2024). Therefore, the antioxidant and anti-inflammatory effects of *Micromeria congesta* plant extract and its protective against LPS-induced liver damage were investigated in the study.

Material and Methods

Plant Extract

Micromeria congesta (MC) plants were collected from their natural habitat and dried. Then, essential fatty acid was obtained from them by hydrodistillation for 6-8 hours using Clevenger apparatus. This essential oil was stored in dark glass bottles at +4°C. Dimethyl sulfoxide (DMSO) was used for homogeneous mixing of the essential oil stock solutions. The essential oil was added to DMSO at a ratio of 1:2 (h:h) to dissolve the essential oil. The mixture of essential oil and DMSO was vortex mixed at 180 rpm for 10 minutes. Stock solutions were stored in the refrigerator at +4°C (Herken et al 2012).

Experimental Design

In this study, 24 adult male Wistar Albino rats weighing 240 ± 20 g were used. All rats were maintained at constant temperature (25 ± 2°C) under a 12 h light/12 h natural light/dark rhythm and were fed a standard laboratory balanced commercial diet and drinking water ad libitum. The animals were randomly divided into 4 groups with 6 rats in each group. This study was conducted with the approval of Harran University Animal Experiments Local Ethics Committee (Protocol Number: 2024/004/16).

Group 1 [Healthy (control, n:6)]: The animals received physiological saline (1 mL/rat/day, orally) simultaneously with the other groups.

Group 2 [LPS (5 mg/kg) (n:6)]: LPS (Sigma, Saint-Quentin-Fallavier, France) at a dose of 5 mg/kg was administered at the end of the seventh day in this group in which no treatment was performed.

Group 3 [*Micromeria congesta* (25 mg/kg) +LPS (5 mg/kg) (n:6)]: 25 mg/kg MC extract was administered by gavage once daily for seven days. At the end of the 7th day, 5 mg/kg LPS was administered 6 hours before euthanasia.

Group 4 [*Micromeria congesta* (50 mg/kg) +LPS (5 mg/kg) (n:6)]: 50 mg/kg MC extract was administered by gavage once daily for seven days. At the end of the 7th day, 5 mg/kg LPS was administered 6 hours before euthanasia. At the end of the 7th day, all animals in the experimental groups were anesthetized and euthanized (Latha et al 2017).

Histopathologic Staining

Liver tissue samples obtained from rats by necropsy were fixed in 10% buffered formaldehyde. The tissues were washed in running tap water and subjected to routine tissue follow-up. The samples were then turned into paraffin blocks. It was taken 4µ thick tissue sections from each paraffin blocked sample by a rotary microtome (Leica RM 2135, Germany). The tissue sections were kept in an oven for a while and then passed through xylol and alcohol series for deparaffinization and rehydration. The tissues were then kept in distilled water and stained with hematoxylin. The tissues were washed to remove excess hematoxylin and stained with eosin. Finally, the sections dehydrated with alcohol and cleaned with xylol were covered with a coverslip with a drop of EntellanTM. The slides were examined under a light microscope (Olympus BX53, Japan) and scored as absent (-), mild (+), moderate (++) and severe (+++) according to the severity of histopathologic findings (Caglayan et al 2019).

Immunohistochemical Staining

Tissue sections taken on adhesive slides were kept in the oven for a while and then passed through xylol and alcohol series for deparaffinization and rehydration processes and kept in distilled water. The tissues were then kept in 3% H_2O_2 for inactivation of the endogenous enzyme reaction, washed with PBS, boiled in retrieval solution to release antigens and cooled. The sections washed with PBS were incubated with protein block to prevent nonspecific

Table 1. Scoring of pathological lesions and biomarker expressions observed in the experimental groups

	D	N	ICI	H	TNF-α	IL-2	HSP-27
Group 1	-	-	-	-	-	-	-
Group 2	+++	++	+++	+++	+++	++	+++
Group 3	+++	+	++	++	+++	+	++
Group 4	++	-	+	++	++	+	+

D. Degeneration N. Necrosis ICI. Inflammatory cell infiltration H. Hyperemia

antigen binding after being bordered with PAP pen. The tissues were then incubated with TNF-α (sc-52B83, Santa Cruz, USA), IL-2 (sc-133118, Santa Cruz, USA) and HSP-27 (sc-13132, Santa Cruz, USA) primary antibodies for 16 hours at +4 ºC, washed with PBS and incubated with biotinized secondary antibody. The tissues washed with PBS were finally incubated with streptoavidin peroxidase. To observe the immunoreaction in the tissues washed with PBS, 3,3' Diaminobenzidine (DAB) chromogen was dropped. The sections, which were then stained with Mayer's Hematoxylin on the back ground, were dehydrated in alcohol, cleared with xylol, dripped with EntellanTM and covered with a coverslip. The slides were examined under a light microscope (Olympus BX53, Japan) and scored as absent (-), mild (+), moderate (++) and severe (+++) according to the severity of immunoreactions (Caglayan et al 2019).

Results

Histopathologic Examination

Histopathologic examination showed that the control group had a normal histologic appearance and no pathologic findings (Figure 1A). Severe histopathologic findings were observed in the LPS group. Severe degenerative and necrotic changes were observed in hepatocytes. The degenerations in hepatocytes were mostly hydropic in character and partial accumulation of fat vesicles was observed. It was noted that cell damage was more severe in the center of the hepatic lobules and decreased towards the periphery. In sometimes, severe degeneration around the central vein was found to be accompanied by coagulative necrosis. Severe dissociation was seen in the radial arrangement extending from the center of hepatocytes to the periphery (hepatic dissociation). Inflammatory cell infiltrations were mostly located perivascularly in the center of the hepatic lobe. Inflammatory cell infiltrations consisting mostly of mononuclear leukocytes were observed in the sinusoidal spaces. The vessels were extremely hyperemic and hemorrhages were also observed in the parenchymal tissue where the inflammatory reaction was severe (Figure 1B). In the 25 mg group, patholgic changes were not as severe as in the LPS group, but degenerative, partially necrotic changes were observed. This was also accompanied by inflammatory cell infiltrations. It was noted that dissociation and vascular changes were less in this group compared to the LPS group (Figure 1C). In the 50 mg group, necrosis was not observed and degenerative changes were less than in the LPS and 25 mg groups. Weak inflammatory reaction, few inflammatory cell infiltration and mild hyperemia were observed, while hemorrhage was not observed (Figure 1D). It was determined that the MC extract groups, the severity of histopathologic lesions decreased in parallel with the dose increase compared to the LPS group. The severity of histopathological findings observed in the groups is presented in Table 1.

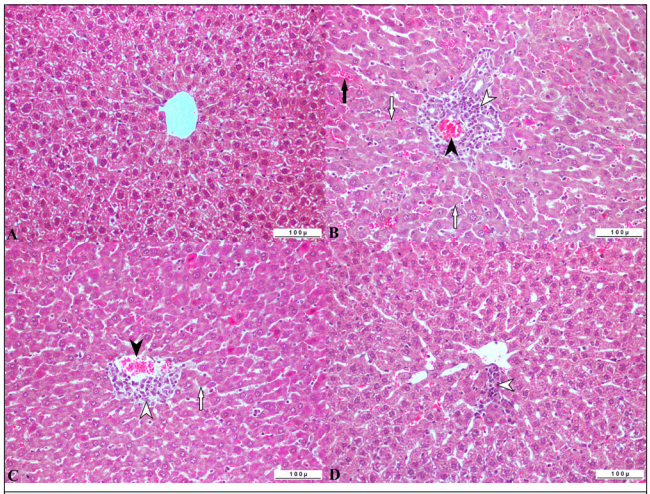

Figure1. Histopathological findings in liver of experimental groups, HE, X200 A. Control group, normal histological appearance B. LPS group, hyperemia in vessels (arrowhead), inflammatory cell infiltration (hollow arrowhead), hemorrhage in parenchyma (arrow), deneration and necrosis in hepatocytes (hollow arrows) C. 25 mg group, hyperemia in vessels (arrow head), inflammatory cell infiltration (hollow arrow head), degeneration in hepatocytes (hollow arrow) D. 50 mg group, inflammatory cell infiltration (hollow arrowhead).

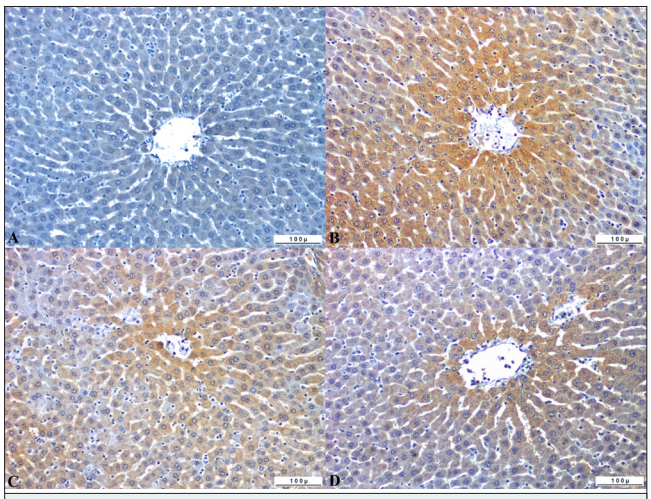

Figure 2. TNF-α immunoreactivities in liver tissue of experimental groups, IHC, X200 A. Control group, TNF-α immunonegative B. LPS group, severe TNF-α expression C. 25 mg group, moderate TNF-α expression D. 50 mg group, mild TNF-α expression.

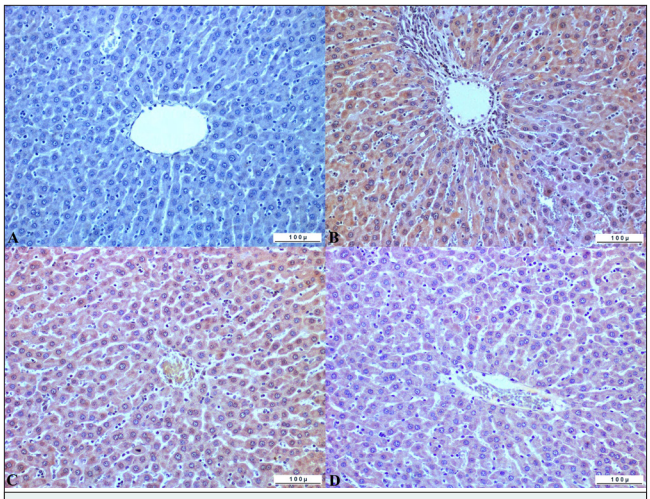

Figure 3. IL-2 immunoreactivities in liver tissue of experimental groups, IHC, X200 A. Control group, IL-2 immunonegative B. LPS group, severe IL-2 expression C. 25 mg group, moderate IL-2 expression D. 50 mg group, mild IL-2 expression.

Immunohistochemical Staining

In the immunohistochemical examinations of the experimental groups samples showed TNF-α and IL-2 expression for inflammation and HSP-27 expression for oxidative stress. TNF-α, IL-2 and HSP27 immunopositivity was not observed in the control group (Figure 2A, 3A, 4A). Severe TNF-α, IL-2 and HSP-27 expressions were observed in the LPS group (Figure 2B, 3B, 4B). In the 25 mg group, weaker expression of TNF-α, IL-2 and HSP 27 was observed compared to the LPS group (Figure 2C, 3C, 4C). In the 50 mg group, mild TNF-α, IL-2 and HSP 27 expression was observed compared to the 25 mg group, although limited in the pericentral region (Figure 2D, 3D, 4D). It was observed that TNF-α and IL-2 expressions, which are important inflammation biomarkers, decreased in the MC extract groups compared to the LPS group in parallel with the increasing dose. Similarly, It was determined that the expression of HSP 27, an important oxidative stress biomarker, decreased in the MC extract-treated groups. The immunoreaction intensities of biomarkers of inflammation and oxidative stress in the groups are presented in Table 1.

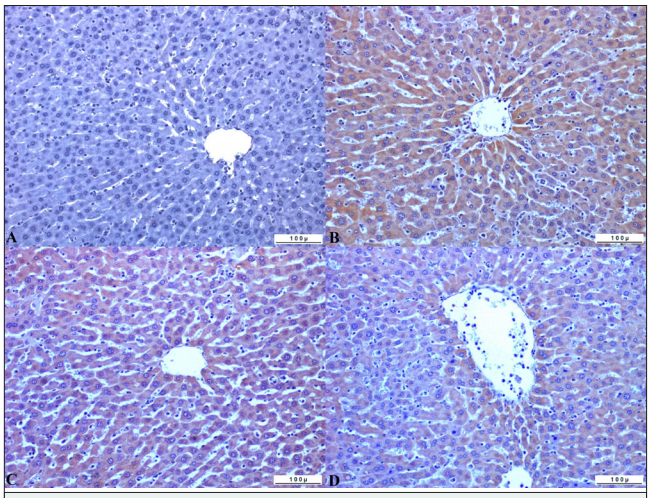

Figure 4. HSP-27 immunoreactivities in liver tissue of experimental groups, IHC, X200 A. Control group, HSP-27 immunonegative B. LPS group, severe HSP-27 expression C. 25 mg group, moderate HSP-27 expression D. 50 mg group, mild HSP-27 expression.

Discussion

Sepsis ranks among the leading causes of death worldwide. In addition to symptomatic and supportive treatments for sepsis, alternative treatment options should be investigated (Furman et al 2019). The liver is one of the most affected organs in systemic inflammations. It also acts as a mechanical and immune filter within the portal system (Bulut el al 2023, Hotchkiss et al 2005). Liver, one of the organs sensitive to LPS, is one of the important subjects of current studies. Therefore, in this study, the protective effect of MC plant extract against the inflammation and oxidative damage caused by LPS in the liver was experimentally investigated.

In this study, the possible effect of MC plant extract against liver damage caused by LPS was examined histopathologically. Depboylu et al (2013) reported that LPS increased lymphocyte and neutrophil infiltration in the liver parenchyma of male and female rats. Kim and Ha (2010) reported that LPS caused necrosis around the central vessels and sinusoids of the liver and paeoniflorin reduced these lesions. Liu et al (2015) reported that LPS caused necrosis and inflammatory cell infiltration in liver hepatocytes and Isofraxidin reduced necrosis and leukocyte migration. No study investigating the

histopathologic effect of MC plant extract against LPS-induced liver damage was found in the literature. In this study, it was observed that LPS caused severe leukocyte migration in the liver and destructive effects on the parenchyma, while MC plant extract reduced these effects.

There are studies suggesting that in vitro LPS administration triggers oxidative stress and inflammation (Skibska et al 2023). In many infectious and toxic studies, TNF-α is utilized for monitoring inflammation (Murdaca et al 2015). Masaki et al. (2004) reported that LPS increased TNF-α level in liver tissue and TNF-α level decreased with adiponectin administration. Bayraktutan (2022) reported that 4-hydroxy phenylboronic acid reduced TNF-α production in liver tissue induced by lipopolysaccharide. Tunçer et al. (2022) reported that α-terpineol administration decreased TNF-α level in lipopolysaccharide-induced liver inflammation model. In previous studies, no study was found in which the effect of Micromeria congesta plant extract against LPS-induced liver damage was examined immunohistochemically in terms of TNF-α. In this study, it was determined by immunohistochemical method that LPS administration caused severe TNF-α expression in the liver tissue and this expression decreased with the use of MC plant extract.

Although TNF-α is the most frequently used biomarker of inflammation, interleukins are also preferred in the monitoring of inflammation in current studies. Especially IL-2, which is involved in cellular defense, initiates TNF-α production by activated T cells through a cyclosporine-sensitive pathway (Yang et al 2018). Temel et al (2023) reported that irbesartan inhibited IL-1-β expression in liver injury induced by LPS. Bayraktutan (2022) reported that 4-hydroxy phenylboronic acid decreased IL-1-β and IL-6 production in lipopolysaccharide-induced liver tissue. Tunçer et al. (2022) reported that α-terpineol administration decreased IL-1-β level in lipopolysaccharide-induced liver inflammation model. In previous studies, it was determined that IL-1-β and IL-6 were evaluated in terms of interleukins, but IL-2 was not evaluated. In this study, it was determined by immunohistochemical method that LPS administration caused severe IL-2 expression in the liver tissue and the use of MC plant extract decreased IL-2 expression.

It is known that LPS-induced hepatotoxicity disrupts intracellular redox balance and causes oxidative stress, and oxidative stress induces inflammation (Al-Dossari et al 2020, Ramos-Tovar and Muriel 2020). Zhou et al. (2022) reported that LPS administration in pigs, a good model for human pathological studies, decreased total antioxidant capacity (T-AOC) and glutathione peroxidase (GSH-Px) activities in serum and liver homogenate, and increased malondialdehyde (MDA) in serum and catalase (CAT) and superoxide dismutase (SOD) activities in liver. Jiang et al. (2018) reported that sofocarpine improved hepatic oxidative stress indicators (H_2O_2 and NO) and increased the expression of antioxidant molecules such as SOD, CAT and glutathione (GSH) in LPS-induced liver injury. Sebai et al (2010) reported that resveratrol inhibited LPS-induced lipoperoxidation and depletion of antioxidant enzyme activities such as SOD and CAT but slightly inhibited GPx activity. They also reported that it abolished LPS-induced liver and plasma NO elevation and attenuated endotoxemia-induced hepatic tissue damage. In previous studies, the presence of oxidative stress in LPS-induced liver injury was mostly examined in serum and tissue homogenates, whereas no study was found in which the expression of oxidative damage in tissue was monitored by immunohistochemical method. In this study, it was determined by immunohistochemical method that LPS administration caused severe HSP 27 expression in liver tissue and the use of MC plant extract reduced HSP 27 expression.

Conclusion

The results of the study showed that LPS caused serious histopathological changes in liver tissue. It was also determined that LPS increased inflammation and oxidative stress in the liver. However, MC plant extract application eliminated LPS-induced histological damage and immunohistochemical examination showed that it had to provided an protective effect against LPS by reducing inflammation and oxidative stress. More studies are needed for MC to be an alternative in the treatment of sepsis.

Declarations

Competing Interests

The authors declared that there is no conflict of interest.

Availability of Data and Materials

The data that support the findings of this study are available on request from the corresponding author.

Ethical Statement

The study was approved by the Harran University Animal Experiments Local Ethics Committee (Protocol Number: 2024/004/16).

Author Contributions

Motivation/Concept: MBD, MD; Design: MD, FSK; Control/Supervision: MBD, FSK; Data Collection and Processing: MBD, MD, FSK; Analysis and Interpretation: MD, FSK; Literature Review: MD; Writing the Article: MBD; Critical Review: FSK

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